Analytical and Numerical Studies of One-Dimensional Poisson-Nernst-Planck Models for Ion Channels

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Abstract

Ion channels are a group of transmembrane proteins that allow passage of ions from one side of the membrane to the other. The physiological event of ion transport is modeled by the Poisson-Nernst-Planck (PNP) system. We study the PNP system in presence of two or three types of ions with certain regions of the inside surface of the channel containing permanently charged amino acid side chains. A singular parameter ε, related to the Debye length, is presented in the PNP system. In the case of two ions, the boundary conditions for the charged region can be specifically solved by solving a scaled algebraic equation. These conditions are then used to solve the PNP system numerically. Multiple solutions emerge from the computation and are probably indicative of more complex functions of ion channels. For ion channels baring three types of ions, the analytical equations are more complicated but the system can be solved using numerical approaches and examples of these results are presented in this paper. The PNP system contains information of the current-voltage (I-V) relations of ion channels when reaching steady-state. Analysis of the I-V property is shown and some representative results discussed.

Acknowledgements

I would like to thank my advisor Dr. Weishi Liu. Dr. Liu has taught me more than just mathematical skills during the course of my graduate study. I joined the program with very limited training in mathematics and extremely poor understanding of research in math. I was able to achieve many goals and successes under his guidiance and with his encouragement. We share tremendous interest and passion in bridging applied mathematics and biology. In doing what we love, Dr. Liu showed me qualities of a science researcher. I will continue to look up to him as a role model in the future as I grow into a scientist.

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I would like to thank my wife, Xin Wang, who has given me endless support during my graduate career. Lastly, I would like to dedicate this thesis to my grandmother, Huiqin Sun, who taught mathematics for 40 years in her life. She was my first math teacher and really the source of my inspiration when studying mathematics. I did not choose math as my major in college but I wish, with my achievement in mathematics, she could not be more proud of me.

Contents

List of Figures

Chapter 1

Introduction

1.1 Ion channels

Biological membranes are essential for cell structures and cellular functions. Cells rely on biological membranes to maintain shape, to partition different compartments, and to communicate with other cells or transport biological materials. The architecture of biological membranes is composed of lipids as well as proteins. Membrane proteins are associated with lipid bilayer matrix through the *fluid mosaic model* proposed by S. Jonathan Singer and Garth Nicolson in 1972. Membrane proteins are divided into three categories: integral membrane proteins (or intrinsic proteins), lipid-linked proteins, and peripheral proteins (or extrinsic proteins)([25]). All living cells must acquire raw materials from their surroundings to synthesize building molecules and to produce energy. Although the unique construction (nonpolar cores of lipid bilayer) of membranes allows the permeation of some small uncharged and nonpolar molecules, biological membranes are highly impermeable to most ionic or polar molecules. These molecules enter and exit cells through the actions mediated by transport proteins. In some cases, transport proteins simply facilitates the diffusion flow of a certain solute

resulting from its own concentration gradient across the membrane. In other cases, solutes are transported against the concentration gradients, during which, energy is often consumed and solutes are pumped through cell membrane by particular carrier proteins.

Ions (such as Na^+, K^+, Ca^{2+}, and Cl^-) play essential physiological roles in biosynthesis, biomatabolism, and signal transduction. Ions are relatively small in size, permanently charged, and highly mobile in aqueous environment. Because of these features, ions often can not diffuse through hydrophobic inner structure of membranes freely. While sometimes ions can move across membranes via ionophores, small molecules that mask the charge of ions and allow them to diffuse through the lipid bilayer, more frequently, the transportation of ions through biological membranes is mediated by a group of membrane bound proteins, ion channel proteins (or ion channels). The $X-$ ray crystal structure of a $Na-K$ ATPase is shown in Figure 1.1. Most ion channel proteins have a cylindrical hollow channel that is embedded in the lipid bilayer. The inside of the channel is relatively hydrophilic, which facilitates the binding of small ions.

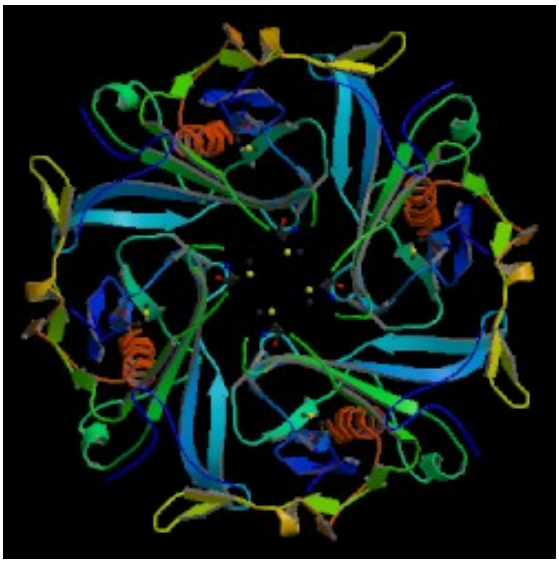

Figure 1.1. General structure of ion channel. Top view of the crystal structure of a potassium channel (PDB ID: 1N9P).

Biological membranes divide up two aqueous compartments both physically and chemically. When ions move across the membrane, a transmembrane electrical difference, defined as membrane potential, is built. $\phi(in)$ - $\phi(out)$ (measured in volts or millivolts) is commonly used to denote the transmembrane potential. The direction of spontaneous ion flow is dictated by the electrochemical potential of the particular ion across the membrane. The driving force (G_Δ) is described as:

$$G_\Delta = RTln\left(\frac{C(in)}{C(out)}\right) + ZF(\phi(in) - \phi(out)), \tag{1.1}$$

where R is the gas constant, T the absolute temperature, Z the charge of the ion, and F the Faraday constant. When G_Δ is negative, the movement of ion is favored. When G_Δ is positive, extra energy is required to overcome the energy barrier in order to move the ion across the membrane in the particular direction. The membrane potential of a cell at a given time results from types and numbers of ion channels open ([20]). Movements of ions with different sizes and charges are often regulated selectively by types of ion channels. Most ion channels are gated by ligand (ligand binding is required to open the channel) or by voltage (certain voltage intensity is required to open the channel). In this paper, gating process will not be discussed and only open channel behavior will be considered.

1.2 Poisson-Nernst-Planck Model

Poisson-Nernst-Planck (PNP) equations, derived from the Boltzmann Equations ([3, 24]), have been used extensively and successfully to model ion flow through membrane channels or charge transport in semiconductors (for example [3, 4, 18, 22]). In this case the PNP equations serve as a mathematical model to describe behaviors

of ions when moving through a tubular-like chanel ([19]). In the context of ions flow through a membrane, the flow of ions is driven by their concentration gradients and by the electric field modeled together by the Nernst-Planck equations, and the electric field is in turn affected by the concentrations governed by the Poisson equation. The one-dimensional PNP system for the flow of n ion species takes the following dimensionless form

$$\begin{aligned} \varepsilon^2 \frac{\partial^2 \phi}{\partial x^2} &= -\sum_{i=1}^{n} \alpha_i c_i, \quad \frac{\partial c_i}{\partial t} + \frac{\partial \bar{J}_i}{\partial x} = 0, \\ D_i \left(\frac{\partial c_i}{\partial x} + \alpha_i c_i \frac{\partial \phi}{\partial x} \right) &= -\bar{J}_i, \end{aligned} \tag{1.2}$$

with the boundary conditions

$$\phi(0) = v_0, \quad c_i(0) = L_i, \quad \phi(1) = 0, \quad c_i(1) = R_i. \tag{1.3}$$

Here ϕ is the electric potential; for $i = 1, 2, ...n$, c_i is the concentration of the i-th ion with valence α_i (positive or negative but pairwise distinct); $\bar{J}_i$ is the flux density of the i-th ion; x is the displacement along the membrane channel normalized from $x = 0$ to $x = 1$; D_i is the diffusion constant of the $i-th$ ion relative to the membrane channel; and the parameter ε is related to the ratio of the Debye length to a characteristic length scale.

Many mathematical works have been done on the existence, uniqueness and qualitative properties of solutions of the boundary value problems even for high dimensional systems and numerical algorithms have been developed toward approximating solutions (see [14, 16, 17, 21] etc.). Under the assumption that $\varepsilon \ll 1$, the problem can be viewed as a singularly perturbed one. In particular, for $n = 2$ and $\alpha_1 = -\alpha_2 = 1$, the boundary value problem was studied in [4] using the method of matched asymptotic expansions

as well as numerical simulations, which provide a good quantitative understanding of the problem.

1.3 Singular Perturbation

Singular Perturbation (SP) is a widely used technique in modern research such as quantum mechanics and semiconductor research ([23]). SP is a type of problem that contains a small parameter (defined as ε). The problem can be studied under different scales. Here we use an example to demonstrate basic dynamic set ups of a singular perturbation system.

Consider the following equation:

$$\varepsilon \frac{dx}{dt} + x - 1 = 0,$$

with the initial condition

$$x(0) = 0.$$

When $\varepsilon \to 0$, the system becomes what is reffered as the slow system:

$$x = 1,$$

with a solution (slow orbit) of

$$x(t) = 1.$$

On the other hand, when ε is not 0, the system (fast system) can be solved as:

$$x(t) = 1 - e^{-\frac{t}{\varepsilon}}.$$

This is considerred to be the singular orbit. By analyzing the slow and singular orbits, in some cases, a smooth solution to the system can be found to connect both orbits.

1.4 Numerical Methods

The numerical analysis utilized in this study deal with a nonlinear system with time steps. The time step in this case represents the process of an event of ion transport from formation of an open channel to a steady-state (or equilibrium) process. The whole process, in nature, has a time span in the order of milliseconds. The time that it takes to reach steady-state, however, is not neglectable in numerical simulations. Here we use a method derived from the Newton's methods and the schematic numerical set-up is demonstrated as following:

$$F(Z) + G(Z) = 0, \tag{1.4}$$

where F is a linear function and G is a nonlinear function of the vector $Z = (z_1, z_2, ..., z_n)^T$. Newton's method for n equations with n variables is given by

$$Z^{(k+1)} = Z^k + H^k, \quad H = (h_1, h_2, ..., h_n)^T,$$

where k represents the schematic step and H is the stepwise difference in Z. When H^k is small,

$$F(Z^k + H^k) \approx F(Z^k) + DF(Z^k)H^k. \tag{1.5}$$

After combining equations (1.4) and (1.5), one has

$$DF(Z^k)H^k \approx G(Z^k) - G(Z^k + H^k). \tag{1.6}$$

At each step of simulation with known Z^k, the first column of $DF(Z^k)$ is calculated by inputting $H = (\delta, 0, 0, ..., 0)^T$ into equation (1.6), where $0 < \delta \ll 1$. Then the n-th column of $DF(Z^k)$ can be calculated using the same approach but letting only the n-th element of H be δ.

The finite element principles are applied in this study. The length of an ion channel is considered to be $x \in [0,1]$ and this unit length is devided into 90 evenly distributed intervals with a stepsize of h (i.e. $x_n - x_{n-1} = h$, for $1 < n \leq 91$). At any point, x_n, we set the following approximations over space:

$$\frac{\partial^2 Z}{\partial x^2} = \frac{Z_{n-1} - 2Z_n + Z_{n+1}}{h^2},$$
$$\frac{\partial Z}{\partial x} = \frac{Z_{n+1} - Z_{n-1}}{2h}.$$

Since the PNP system contains time dependent elements, we then treat the system with a two-step calculation. Consider the time-dependent part as a linear function $F(Z,t)$ and the remaining part a nonlinear function $G(Z)$. The initial values of each step are given as Z^k where $Z = (\phi, c_1, c_2)^T$ and $t^{k+1} - t^k = dt$. The PNP system can be written as:

$$F(Z^k, t^k) + G(Z^k) = 0. \tag{1.7}$$

$DF(Z^k, t^k)$ is then computed as mentioned in equation (1.6), and H^k is then computed

by solving the linear equation:

$$DF(Z^k, t^k)H^k = G(Z^k),$$

assuming $G(Z^k + H^k) \approx 0$. Z^k is reset to be $Z^k + H^k$ and the computation is repeated until $\left|H^k\right| \leq 10^{-6}$. Now we let $t^{k+1} = t^k + dt$, the iteration is repeated to resolve Z^{k+1}. A total time T is applied to allow iterations to result in $F(Z^k, t^k) \rightarrow 0$, an indication of steady-state behavior.

Chapter 2

Studies of One-Dimensional Poisson-Nernst-Planck Systems when Two Types of Ions are Present

2.1 Analytical Results

We now consider the PNP system with two different types of ions represented in the following equations

$$\begin{aligned} \varepsilon^2 \frac{\partial^2 \phi}{\partial x^2} &= -(\alpha c_1 - \beta c_2 + Q(x)), \\ \frac{\partial c_1}{\partial t} + \frac{\partial J_1}{\partial x} = 0, \quad \frac{\partial c_2}{\partial t} + \frac{\partial J_2}{\partial x} &= 0, \\ D_1 \left(\frac{\partial c_1}{\partial x} + \alpha c_1 \frac{\partial \phi}{\partial x} \right) &= -J_1, \\ D_2 \left(\frac{\partial c_2}{\partial x} - \beta c_2 \frac{\partial \phi}{\partial x} \right) &= -J_2, \end{aligned} \tag{2.1}$$

with the boundary conditions

$$\begin{aligned} \phi(0) = v_0, \quad c_1(0) = L_1, \quad c_2(0) = L_2, \\ \phi(1) = 0, \quad c_1(1) = R_1, \quad c_2(1) = R_2. \end{aligned} \tag{2.2}$$

For simplicity reasons we take $\alpha = 1$ and -$\beta = -1$ (for example, Na^+ and Cl^-) and ϕ is the electric potential across the membrane. It follows that c_1 and c_2 represent concentrations of the positively charged ion (α) and the negatively charged ion (-β), respectively, while J_1 and J_2 indicate the flux density of these ions. Many ion chanels, if not all, have permanently charged amino acid residues along the ion pathway with, serving as attracting spots which ions can interact with as a result of electrostatic interaction. The interaction also contributes to the change of flux in response to the ion concentrations. Here, $Q(x)$, which was ommitted in equation (1.2), is the permanent charge along the ion chanel that satisfies

$$\begin{aligned} Q(x) = 0 \quad for \quad x\in[0,a), \\ Q(x) = 2Q_0 \quad for \quad x\in[a,b], \\ Q(x) = 0 \quad for \quad x\in(b,1], \\ 0 < a < b < 1, \quad Q_0 \neq 0. \end{aligned} \tag{2.3}$$

A special case has been illustrated in ([9]). In that study, the authors considered the same PNP system described in equation (2.1) with $\alpha = \beta = 1$, and $a = 1/3,\ b = 2/3$. When a dynamical system framework was applied the PNP system was reconstructed into a standard form of singularly perturbed system. The singular orbits for the system

was explicitly analyzed. Here we cite the analytical conclusions:

$$\begin{aligned} F(A) =& e^{K(A)}\left(\sqrt{Q_0^2+A^2}-\frac{Q_0(J_2-J_1)}{6(L-A)}\right) \\ &+\frac{Q_0(J_2-J_1)}{6(L-A)}-\sqrt{Q_0^2+B^2}, \\ J_2-J_1 =& 6(L-A)-\frac{6(L-A)}{\ln\frac{BL}{AR}}\left(v_0+\ln\frac{L_1(\sqrt{Q_0^2+B^2}-Q_0)}{R_1(\sqrt{Q_0^2+A^2}-Q_0)}\right) \\ &-\frac{6(L-A)(\sqrt{Q_0^2+B^2}-\sqrt{Q_0^2+A^2}+L-A}{Q_0\ln\frac{BL}{AR}}, \end{aligned} \tag{2.4}$$

where

$$\begin{aligned} A=\sqrt{c_1^a c_2^a},\quad L=\sqrt{L_1L_2},\quad R=\sqrt{R_1R_2}, \\ K(A)=-6(L-A)\frac{\sqrt{Q_0^2+B^2}-\sqrt{Q_0^2+A^2}+L-A}{Q_0(J_2-J_1)}. \end{aligned}$$

Note that A is expressed in the form of the geometric average of the concentrations of ions at $x=a$. When given the values for $L_1,\ L_2,\ R_1,\ R_2,\ Q_0$ and v_0, equation (2.4) becomes an algebraic function with only one unknown A. The roots of equation $F(A)=0$ can be used to calculate boundary conditions for ϕ, c_1 and c_2 at both $x=a$ and $x=b$. A great value rising from this analysis is that more features of the complex nature of the ion flow can be revealed. In some experiments where single ion channels were isolated and the ion translocation was studied in details ([3,6]), these channels displayed unexpected biphasic behaviors when the solution conditions were kept constant. This could simply be corresponding to the multiple levels of ion accumulation (i.e. ion concentrations) near the charged area inside the channel protein, which, in turn, is indicated by the multiple solutions to the steady-state PNP system mentioned in equation (2.1).

2.2 Numerical Analysis

In this section we demonstrate the numerical analysis of one-dimensional Poisson-Nernst-Planck systems with two types of ions. The implications of the results will be discussed in section 2.4. The PNP equations considerred here are given by

$$\begin{aligned}
\varepsilon^2 \frac{\partial^2 \phi}{\partial x^2} &= -(\alpha c_1 - \beta c_2 + Q(x)), \\
\frac{\partial c_1}{\partial t} + \frac{\partial J_1}{\partial x} = 0, \quad \frac{\partial c_2}{\partial t} + \frac{\partial J_2}{\partial x} &= 0, \\
D_1 \left(\frac{\partial c_1}{\partial x} + \alpha c_1 \frac{\partial \phi}{\partial x} \right) &= -J_1, \\
D_2 \left(\frac{\partial c_2}{\partial x} - \beta c_2 \frac{\partial \phi}{\partial x} \right) &= -J_2.
\end{aligned}$$

We then eliminate J_1 and J_2 and rewrite the system as following

$$\begin{aligned}
\varepsilon^2 \frac{\partial^2 \phi}{\partial x^2} + (\alpha c_1 - \beta c_2 + Q(x)) &= 0, \\
\frac{\partial c_1}{\partial t} - D_1 \left(\frac{\partial^2 c_1}{\partial x^2} + \alpha \frac{\partial c_1}{\partial x} \frac{\partial \phi}{\partial x} + \alpha c_1 \frac{\partial^2 \phi}{\partial x^2} \right) &= 0, \\
\frac{\partial c_2}{\partial t} - D_2 \left(\frac{\partial^2 c_2}{\partial x^2} - \beta \frac{\partial c_2}{\partial x} \frac{\partial \phi}{\partial x} - \beta c_2 \frac{\partial^2 \phi}{\partial x^2} \right) &= 0.
\end{aligned} \tag{2.5}$$

The boundary conditions for the system are:

$$\begin{aligned}
\phi(0) = 0.1, \quad c_1(0) = 2, \quad c_2(0) = 2, \\
\phi(1) = 0, \quad c_1(1) = 5, \quad c_2(1) = 5.
\end{aligned}$$

Permanent charge parameters are:

$$Q(x) = 0 \quad for \quad x\in[0,1/3),$$
$$Q(x) = 2 \quad for \quad x\in[1/3,2/3],$$
$$Q(x) = 0 \quad for \quad x\in(2/3,1].$$

For simplicity reasons we also set $D_1 = D_2 = 1$. When initial and boundary conditions are applied, ϕ, c_1, and c_2 can be solved specifically over a range of x ($[0,1/3]$, $[1/3,2/3]$ and $[2/3,1]$),using numerical approaches. The roots of equation (2.4) are first calculated and the roots are applied one at a time to calculate boundary conditions at $x = 1/3$ and $x = 2/3$. The results illustrated here all result from simulations after a total time of $T = 1000dt$ and each set of results uses one root (A) to equation (2.4).

2.2.1 $\varepsilon = 0.2$, and $A = 2$

See Figure 2.1 for numerical result of potential and ion concentration distribution after reaching steady-state when $A = 2$ and $F(A) = 0$.

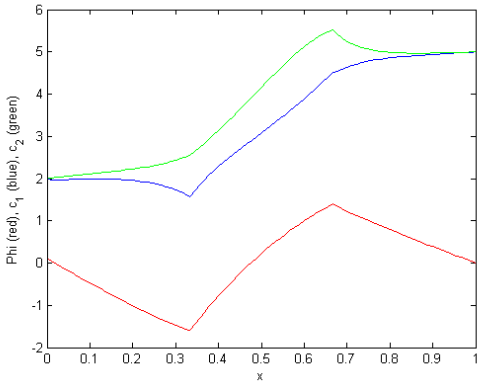

Figure 2.1. First solution for two types of ions. Numerical results of ϕ (red), c_1 (blue) and c_2 (green) for $A = 2$ with $L_1 = L_2 = 2$, $R_1 = R_2 = 5$, $Q = 2$, $v_0 = 0.1$, and $\varepsilon = 0.2$.

2.2.2 $\varepsilon = 0.2$, and $A = 3.005315$

See Figure 2.2 for numerical result of potential and ion concentration distribution after reaching steady-state when $A = 3.005315$ and $F(A) = 0$.

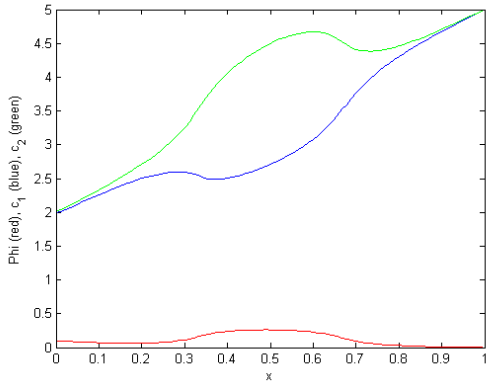

Figure 2.2. Second solution for two types of ions. Numerical results of ϕ (red), c_1 (blue) and c_2 (green) for $A = 3.005315$ with $L_1 = L_2 = 2$, $R_1 = R_2 = 5$, $Q = 2$, $v_0 = 0.1$, and $\varepsilon = 0.2$.

2.2.3 $\varepsilon = 0.2$, and $A = 3.045652$

See Figure 2.3 for numerical result of potential and ion concentration distribution after reaching steady-state when $A = 3.045652$ and $F(A) = 0$.

2.2.4 Stability of the Numerical Solutions

The solution may also be solved by considering the range $x \in [0,1]$ with the boundary conditions listed in equation (2.2). Linear solution guesses are usually given to all calculating points for both c_1 and c_2 as initial values, from which the initial ϕ is computed using the first equation in equation (2.5). It is reasonable to think that only the stable solutions can be reached in this approach. We check the stability of the numerically computed solutions by using the solutions solved with different A values as an initial input (i.e. starting solution for numerical iterations), followed by the

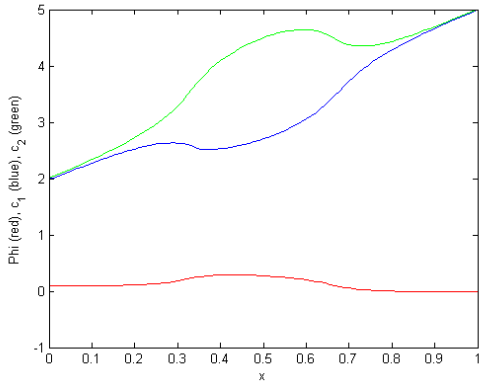

Figure 2.3. Third solution for two types of ions. Numerical results of ϕ (red), c_1 (blue) and c_2 (green) for $A = 3.045652$ with $L_1 = L_2 = 2$, $R_1 = R_2 = 5$, $Q = 2$, $v_0 = 0.1$, and $\varepsilon = 0.2$.

same numerical computation to solve PNP. The results indicate that all solutions listed in Figures 2.1, 2.2 and 2.3 all converge to one stable form, which is shown in Figure 2.4. The stable solution appears to be identical to that of the case when $\varepsilon = 0.2$, and

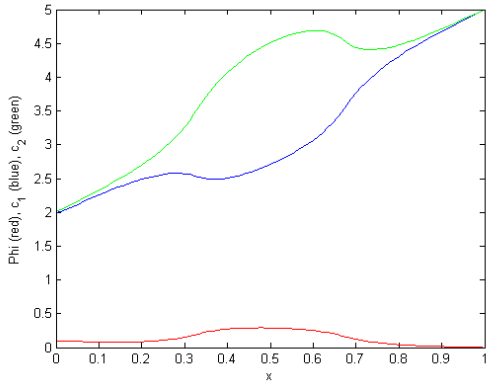

Figure 2.4. Stable solution for two types of ions. ϕ (red), c_1 (blue) and c_2 (green) to the PNP system with two types of ions (1 and -1) and the following boundary conditions: $L_1 = L_2 = 2$, $R_1 = R_2 = 5$, $Q = 2$, $v_0 = 0.1$, and $\varepsilon = 0.2$.

$A = 3.005315$. We conclude that this is the only stable solution among all three when solving the PNP equations numerically.

2.3 Effect of ε on Numerical Solutions

In this section we assess the effects that the magnitude of ε has on the numerically computed solutions to the PNP system in the case of two types of ions. We consider the same system as described in equation (2.5) with the same conditions listed in section 2.2. Here we set up three independent numerical computations with different ε values and the results are listed in the following.

2.3.1 $\varepsilon = 1$

Here we do not have a small ε and the stable numerical solution is shown in Figure 2.5.

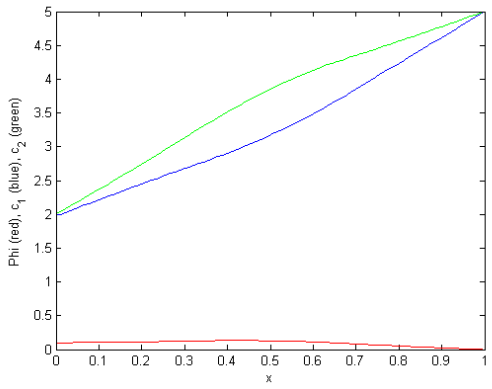

Figure 2.5. Stable solution for $\varepsilon = 1$. ϕ (red), c_1 (blue) and c_2 (green) to the PNP system with two types of ions (1 and -1) and the following boundary conditions: $L_1 = L_2 = 2$, $R_1 = R_2 = 5$, $Q = 2$, $v_0 = 0.1$, and $\varepsilon = 1$.

2.3.2 $\varepsilon = 0.5$

The value of ε is comparable to 1 and the stable numerical solution is shown in Figure 2.6.

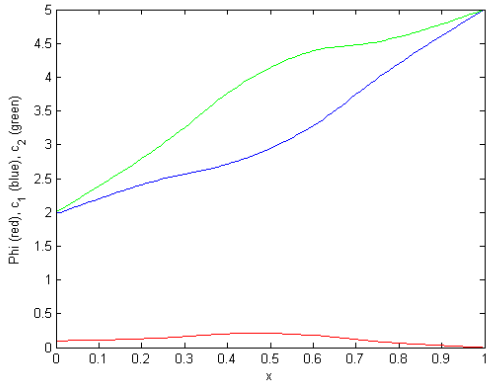

Figure 2.6. Stable solution for $\varepsilon = 0.5$. ϕ (red), c_1 (blue) and c_2 (green) to the PNP system with two types of ions (1 and -1) and the following boundary conditions: $L_1 = L_2 = 2$, $R_1 = R_2 = 5$, $Q = 2$, $v_0 = 0.1$.

2.3.3 $\varepsilon = 0.05$

In this case, $\varepsilon \ll 1$, and the stable numerical solution is shown in Figure 2.7. A clear

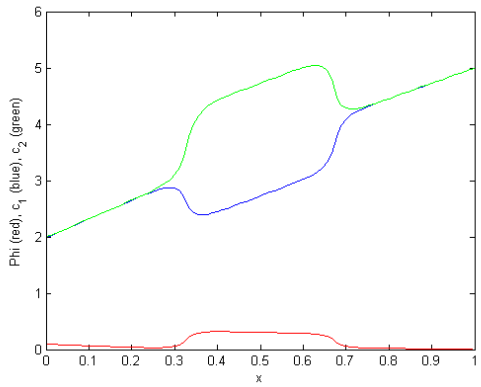

Figure 2.7. Stable solution for $\varepsilon = 0.05$. ϕ (red), c_1 (blue) and c_2 (green) to the PNP system with two types of ions (1 and -1) and the following boundary conditions: $L_1 = L_2 = 2$, $R_1 = R_2 = 5$, $Q = 2$, $v_0 = 0.1$.

trend can be detected here, that is, as $\varepsilon \to 0$ ion concentrations change more sharply at positions where permanent charge distribution changes.

2.4 Remarks

The numerically computed solutions of the one-dimensional PNP system are demonstrated in this chapter. The analytic methods described in ([9]) present a nice treatment in studying the PNP equations with two types of ions. One can utilize the treatment to specifically calculate the boundary conditions at any particular point inside the chennel and, in turn, the numarical solutions to the system can be solved. Some of the solutions are not stable (described in section 2.2) and this could be easily attributed to any of the following reasons:

First, the geometric properties are not considered in this chapter. Protein channels have extremely complicated structures and the inside surface of a channel is solely dependent upon the arrangement of the amino acid side chains as well as their hydration/protonation states. Though a good approximation mathematically, the one-dimensional tubular channel model does not include information on channel shape or inner diameter.

Second, the computational power depends on the total number of finite elements used in the iterations. Some solutions contain rapid changes around the positions where permanent charge is different from the previous point. These solutions can easily converge to the stable one, the attractor, when used as initial guesses. An increase in the number of points at these positions can achieve better apprximation to the natural solution and, therefore, help the unstable solutions survive the computation.

Thrid, the boundary conditions might not be in the vicinity of those that appear in nature. The concentration difference of solutes (ions) across the membrane is often in the order of two magnitudes. The numbers discussed in this chapter are for demonstration reasons.

Lastly, D_1 and D_2 are set to zero in this chapter. They contribute significantly to the

PNP system as they usually differ by the type of ions.

The multiplicity of solutions might be related to the complex behaviors of the ions channels. One phenomenon worth of mentioning is that some of these ion channels display gating properties which allow them to temporarily increase/decrease the ion passage ([2]). The multiple solutions may also indicate the ability of ion channels to selectively allow the translocation of particular type(s) of ion under extreme conditions ([1, 25]).

Chapter 3

Numerical Simulations of the Flow of Three Types of Ions Modeled by One-Dimensional Poisson-Nernst-Planck Systems

Three types of ions (for example, K^+, Ca^{2+} and Cl^-) can be found to translocate the cell membrane simultaneously through a chennel ([1]). The PNP system is redefined as

$$\begin{aligned}
\varepsilon^2 \frac{\partial^2 \phi}{\partial x^2} + (\alpha c_1 - \beta c_2 + \gamma c_3 + Q(x)) &= 0, \\
\frac{\partial c_1}{\partial t} - \left(\frac{\partial^2 c_1}{\partial x^2} + \alpha \frac{\partial c_1}{\partial x} \frac{\partial \phi}{\partial x} + \alpha c_1 \frac{\partial^2 \phi}{\partial x^2} \right) &= 0, \\
\frac{\partial c_2}{\partial t} - \left(\frac{\partial^2 c_2}{\partial x^2} - \beta \frac{\partial c_2}{\partial x} \frac{\partial \phi}{\partial x} - \beta c_2 \frac{\partial^2 \phi}{\partial x^2} \right) &= 0, \\
\frac{\partial c_3}{\partial t} - \left(\frac{\partial^2 c_3}{\partial x^2} + \gamma \frac{\partial c_3}{\partial x} \frac{\partial \phi}{\partial x} + \gamma c_3 \frac{\partial^2 \phi}{\partial x^2} \right) &= 0,
\end{aligned} \tag{3.1}$$

where

$$\alpha = 1, \quad -\beta = -1, \quad \gamma = 2,$$

3.1 Numerical Results when the Net Charge is Zero at Boundaries

We first apply the boundary conditions

$$\phi(0) = 0.1, \quad c_1(0) = 10, \quad c_2(0) = 20, \quad c_3(0) = 5,$$
$$\phi(1) = 0, \quad c_1(1) = 4, \quad c_2(1) = 10, \quad c_3(1) = 3.$$

Permanent charge parameters are:

$$Q(x) = 0 \quad for \quad x\in[0,1/3),$$
$$Q(x) = -20 \quad for \quad x\in[1/3,2/3],$$
$$Q(x) = 0 \quad for \quad x\in(2/3,1].$$

When $\varepsilon = 0.2$ and $T = 1000dt$, the stable numerical solutions are computed and shown in Figure 3.1.

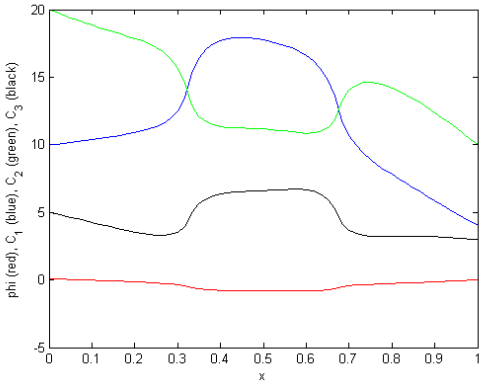

Figure 3.1. Stable solution for even boundary conditions. ϕ (red), c_1 (blue), c_2 (green) and c_3 (black) to the PNP system with three types of ions (1, -1 and 2).

3.2 Numerical Results when the Net Charge is not Zero at Boundaries

In this case the boundary conditions are

$$\phi(0) = 0.1, \quad c_1(0) = 10, \quad c_2(0) = 20, \quad c_3(0) = 3,$$
$$\phi(1) = 0, \quad c_1(1) = 4, \quad c_2(1) = 10, \quad c_3(1) = 10.$$

Permanent charge parameters are:

$$Q(x) = 0 \quad for \quad x\in[0,1/3),$$
$$Q(x) = -20 \quad for \quad x\in[1/3,2/3],$$
$$Q(x) = 0 \quad for \quad x\in(2/3,1].$$

The stable numerical solutions when $\varepsilon = 0.2$ and $T = 1000dt$ are shown in Figure 3.2.

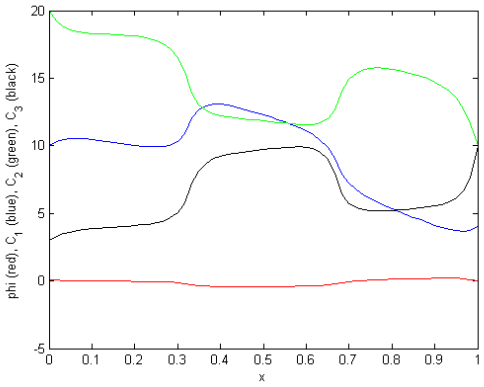

Figure 3.2. Stable solution for uneven boundary conditions. ϕ (red), c_1 (blue), c_2 (green) and c_3 (black) to the PNP system with three types of ions (1, -1 and 2).

When the ion concentrations do not favor electrostatic neutrality, the formation of a layer (for example, c_3 in Figure 3.2) can be seen in the solution near boundaries (i.e. where concentrations change rapidly). This phenomenon has been described before

([19]) due to the contribution from a small value of ε. This chapter shows that the flow of three types of ions through a single channel can be solved numerically. The results like those shown in Figures 3.1 and 3.2 can be used to characterize ion flow as well as more detailed medel of the channel itself including its capacity to transport ions under steady-state conditions. The two sets of boundary conditions only differ in the concentrations of one ion. The solutions, however, display marked differences within the regions of permanent charges. This might be related to the ion selectivity of the channels, which is often mediated by the permanent charges found inside the channels ([1, 25]). It is practically challenging to identify ion distributions inside the channels when using experimental methods. The numerical methods presented in this chapter might become particularly valuable to gain more information on the physiological roles of the permanent charges. Another important characterization of ion channels in experimental physiology is to measure the current-voltage (I-V) relation of a specific type of ion chennel. This topic is to be discussed in the following context.

Chapter 4

I-V Relations of Poisson-Nernst-Planck Governed Ion Channels

The current-voltage (I-V) relation is a trademark measuremnt of ion channel behavior in response to the electrostatic potential ([6, 20, 22, 25]). The I-V profile usually represents the ability of an ion channel to continuously and selectively allow flow of ions. Methods of studying I-V relation have been extremely well established in experimental biology (for examples [5, 7, 8, 10–13, 15])

In ([9]), a one-dimensional steady-state Poisson-Nernst-Planck system was analyzed in the framework of geometric singular perturbation theory of dynamical systems. It is assumed that the permanent charge is known and is piecewise constant. Treating the Debye length as a singular parameter, the zeroth order behavior of the PNP system can be completely understood. In particular, the zeroth order I-V relation can be derived. In fact, all the internal dynamics and the I-V relation are reduced to a set of algebraic equations. A great advantage of the results is the simplicity (and 'accuracy' supported by this work for some channels).

4.1 Analytical results

The analytical results are obtained through the one-dimensional PNP systems of the form:

$$\begin{aligned} &\frac{1}{h(x)}\frac{d}{dx}\left(\varepsilon_0^2(x)h(x)\frac{d}{dx}\bar{\phi}(x)\right) = -e\left(\sum_{i=1}^{n}\alpha_i c_i + Q(x)\right), \quad \frac{d\bar{J}_i}{dx} = 0, \\ &-\bar{J}_i = \frac{1}{kT}D_i(x)h(x)c_i(x)\frac{d}{dx}\left(kT\ln\frac{c_i(x)}{c_0} + \alpha_i e\bar{\phi}(x)\right), \quad i = 1,\cdots,n \end{aligned} \tag{4.1}$$

with the boundary conditions

$$\bar{\phi}(0) = \bar{v}_0, \quad c_i(0) = L_i; \quad \bar{\phi}(1) = 0, \quad c_i(1) = R_i. \tag{4.2}$$

Here, for $i = 1,\cdots,n$, $c_i(x)$ is the density of the i-th ion species with valence α_i, $D_i(x)$ the diffusion coefficient, $\bar{J}_i$ the flux density, $Q(x)$ is the permanent charge along the channel, $h(x)$ is the cross-section area, $\varepsilon^2(x)$ is the dielectric coefficient, $\bar{\phi}$ the electric potential, c_0 is some (constant) characteristic density.

We will consider $n = 2$, $\alpha_1 > 0$ and $\alpha_2 < 0$, and assume D_i and ε_0 are constant. The current is thus $I = \alpha_1\bar{J}_1 + \alpha_2\bar{J}_2$. Our purpose is to examine the I-V relation; that is, the dependence of I on $\bar{v}_0$ for given L_i and R_i.

With the following rescaling

$$J_i = \frac{\bar{J}_i}{D_i}, \quad \phi = \frac{e}{kT}\bar{\phi}, \quad \varepsilon^2 = \frac{kT}{e^2}\varepsilon_0^2, \quad v_0 = \frac{e}{kT}\bar{v}_0,$$

system (4.1) together with the boundary condition (4.2) become

$$\begin{aligned} \frac{\varepsilon^2}{h(x)}\frac{d}{dx}\left(h(x)\frac{d}{dx}\phi\right) &= -\alpha_1 c_1 - \alpha_2 c_2 - Q(x), \quad \frac{dJ_i}{dx} = 0, \\ -J_1 = h(x)\left(\frac{dc_1}{dx} + \alpha_1 c_1 \frac{d\phi}{dx}\right), &\quad -J_2 = h(x)\left(\frac{dc_2}{dx} + \alpha_2 c_2 \frac{d\phi}{dx}\right), \end{aligned} \tag{4.3}$$

with the boundary conditions

$$\phi(0) = v_0, \quad c_i(0) = L_i; \quad \phi(1) = 0, \quad c_i(1) = R_i. \tag{4.4}$$

In [9], the problem (4.3) and (4.4) was analyzed with the assumption that ε is small. We will use the analytical results to derive an approximation of the I-V relation and compare it with the experimental data.

Note that system (4.3) does not dependent on the specific type of ions except the valences. The contribution of the finite sizes of different ions with same valences does appear in the I-V relations via the diffusion coefficients as

$$I = \alpha_1 \bar{J}_1 + \alpha_2 \bar{J}_2 = D_1 \alpha_1 J_1 + D_2 \alpha_2 J_2.$$

Whether or not the contribution of the finite sizes of ions in terms of diffusion coefficients to the I-V is more significant comparing to other forms of effects is a central concern of this chapter.

In this chapter, we will consider the case where the outer regions are reservoirs and the permanent charge has $m \geq 3$ constant values along the channel; that is, for a partition $x_0 = 0 < x_1 < x_2 < \cdots < x_m = 1$, $Q(x) = 0$ for $x \in (x_0, x_1) \cup (x_{m-1}, x_m)$ where the two intervals represent the two reservoirs at the end of the channel, and $Q(x) = Q_j$ for $x \in (x_{j-1}, x_j)$.

4.1.1 $\alpha_1 = 1$, $\alpha_2 = -1$ and $m = 3$.

Suppose $Q(x) = 0$ for $x \in (0,a) \cup (b,1)$ and $Q = 2Q_0$ for $x \in (a,b)$. Under the electronetruality assumption at both ends; that is $L_1 = L_2 = L$ and $R_1 = R_2 = R$, we have (see [9] for details) that the zeroth order I-V relation is given by

$$I = \alpha_1 D_1 J_1 + \alpha_2 D_2 J_2 = \frac{L-A}{\int_0^a h^{-1}(s)ds} \left(\frac{(D_1+D_2)U}{\ln \frac{BL}{AR}} - 2D_2 \right), \tag{4.5}$$

where

$$B = \frac{\int_b^1 h^{-1}}{\int_0^a h^{-1}}(L-A) + R,$$

$$U = v_0 + \ln \frac{L(\sqrt{Q_0^2+B^2} - Q_0)}{R(\sqrt{Q_0^2+A^2} - Q_0)} + \frac{\sqrt{Q_0^2+B^2} - \sqrt{Q_0^2+A^2}}{Q_0} + \frac{(L-A)\int_a^b h^{-1}}{Q_0 \int_0^a h^{-1}},$$

$$J_1 = \frac{L-A}{\int_0^a h^{-1}(s)ds} \frac{U}{\ln \frac{BL}{AR}}, \quad J_2 = \frac{L-A}{\int_0^a h^{-1}(s)ds} \left(2 - \frac{U}{\ln \frac{BL}{AR}} \right),$$

and A is determined by

$$F(A) = 0 \tag{4.6}$$

where

$$\begin{aligned} F(A) = & e^{-(J_1+J_2)y_0} \left(\sqrt{Q_0^2+A^2} - Q_0 \right) - \left(\sqrt{Q_0^2+B^2} - Q_0 \right) \\ & - \frac{2Q_0 J_1}{J_1+J_2} \left(1 - e^{-(J_1+J_2)y_0} \right), \end{aligned} \tag{4.7}$$

$$y_0 = \frac{(L-A)\int_a^b h^{-1}(s)ds}{(J_2-J_1)Q_0\int_0^a h^{-1}(s)ds} + \frac{\sqrt{Q_0^2+B^2}-\sqrt{Q_0^2+A^2}}{(J_2-J_1)Q_0} > 0.$$

4.1.2 $\alpha_1 = 1$, $\alpha_2 = -1$ and $m = 5$.

Suppose $Q(x) = 0$ for $x \in (0,x_1) \cup (x_2,x_3) \cup (x_4,1)$,$Q = 2Q_2$ for $x \in (x_1,x_2)$ and $Q = 2Q_4$ for $x \in (x_3,x_4)$. For $1 \le j \le 5$, set $H_j = \int_{x_{j-1}}^{x_j} h^{-1}(s)ds$, and $z_j^2 = c_1^{[j]}c_2^{[j]}$ for $j = 1,2,3,4$ at landing points where $Q(x)$ changes. We have,

$$J_1 = \frac{(L-z_1)(v_0 - \phi^{[1]} + \ln L - \ln c_1^{[1]})}{H_1(\ln L - \ln z_1)}, \quad J_2 = \frac{2(L-z_1)}{H_1} - J_1,$$

where

$$\begin{aligned}\phi^{[1]} =& \frac{H_5(L-z_1)(\ln z_4 - \ln R)(v_0 + \ln L - \ln c_1^{[1]})}{H_1(z_4-R)(\ln L - \ln z_1)E} \\ &+ \frac{(\ln z_2 - \ln z_3)(v_0 + \ln L - \ln c_1^{[1]})}{H_3(\ln L - \ln z_1)E} \\ &+ \frac{\ln R - \ln c_1^{[4]} + \ln c_1^{[3]} - \ln c_1^{[2]}}{E} \\ &+ \frac{H_1(z_3-R) - (H_4+H_5)(L-z_1)}{H_1Q_4E} \\ &+ \frac{H_1(z_1-z_3) - (H_1+H_2)(L-z_1)}{H_1Q_2E},\end{aligned}$$

$$E = 1 + \frac{\ln z_2 - \ln z_3}{H_3(\ln L - \ln z_1)} + \frac{H_5(L-z_1)(\ln z_4 - \ln R)}{H_1(z_4-R)(\ln L - \ln z_1)},$$

$$c_1^{[1]} = \left(\sqrt{Q_2^2+z_1^2}-Q_2\right)\exp\left\{\frac{\sqrt{Q_2^2+z_1^2}-z_1}{Q_2}\right\},$$
$$c_1^{[2]} = \left(\sqrt{Q_2^2+z_2^2}-Q_2\right)\exp\left\{\frac{\sqrt{Q_2^2+z_2^2}-z_2}{Q_2}\right\},$$
$$c_1^{[3]} = \left(\sqrt{Q_4^2+z_3^2}-Q_4\right)\exp\left\{\frac{\sqrt{Q_4^2+z_3^2}-z_3}{Q_4}\right\},$$
$$c_1^{[4]} = \left(\sqrt{Q_4^2+z_4^2}-Q_4\right)\exp\left\{\frac{\sqrt{Q_4^2+z_4^2}-z_4}{Q_4}\right\},$$

$$z_2 = z_3 + \frac{H_3}{H_1}(L-z_1), \quad z_4 = R + \frac{H_5}{H_1}(L-z_1),$$

and z_1 and z_3 are determined by

$$F(z_1,z_3) = 0 \text{ and } G(z_1,z_3) = 0, \tag{4.8}$$

where

$$\begin{aligned} F(z_1,z_3) =& e^{-(J_1+J_2)y_1}\left(\sqrt{Q_2^2+z_1^2}-Q_2\right) - \left(\sqrt{Q_2^2+z_2^2}-Q_2\right) \\ & - \frac{2Q_2J_1}{J_1+J_2}\left(1-e^{-(J_1+J_2)y_1}\right), \\ G(z_1,z_3) =& e^{-(J_1+J_2)y_2}\left(\sqrt{Q_4^2+z_3^2}-Q_4\right) - \left(\sqrt{Q_4^2+z_4^2}-Q_4\right) \\ & - \frac{2Q_4J_1}{J_1+J_2}\left(1-e^{-(J_1+J_2)y_2}\right), \end{aligned}$$

and $y_1 > 0$ and $y_2 > 0$ are given by

$$y_1 = \frac{\sqrt{Q_2^2+z_2^2}-z_2-\sqrt{Q_2^2+z_1^2}+z_1}{J_2-J_1} - \frac{H_1(z_1-z_3)-(H_1+H_2)(L-z_1)}{H_1Q_2(J_2-J_1)},$$
$$y_2 = \frac{\sqrt{Q_4^2+z_4^2}-z_4-\sqrt{Q_4^2+z_3^2}+z_3}{J_2-J_1} - \frac{H_1(z_3-R)-(H_4+H_5)(L-z_1)}{H_1Q_4(J_2-J_1)}.$$

We remark that, when $Q_2 = 0$ or $Q_4 = 0$, the above formula should be understood as the corresponding numerator is zero. Then, the result recovers that for the case discussed in Section 4.1.1.

4.1.3 $\alpha_1 = 2$, $\alpha_2 = -1$, and $m = 5$

First of all, we have

$$\begin{aligned}
&\alpha_1 L_1 e^{\alpha_1(v_0-\phi^L)} + \alpha_2 L_2 e^{\alpha_2(v_0-\phi^L)} = 0,\\
&\alpha_1 c_1^{[1]} e^{\alpha_1(\phi^{[1]}-\phi^{[1,1]})} + \alpha_2 c_2^{[1]} e^{\alpha_2(\phi^{[1]}-\phi^{[1,1]})} = 0;\\
&\alpha_1 c_1^{[1]} e^{\alpha_1(\phi^{[1]}-\phi^{[1,2]})} + \alpha_2 c_2^{[1]} e^{\alpha_2(\phi^{[1]}-\phi^{[1,2]})} + 2Q_2 = 0,\\
&\alpha_1 c_1^{[2]} e^{\alpha_1(\phi^{[2]}-\phi^{[2,2]})} + \alpha_2 c_2^{[2]} e^{\alpha_2(\phi^{[2]}-\phi^{[2,2]})} + 2Q_2 = 0;\\
&\alpha_1 c_1^{[2]} e^{\alpha_1(\phi^{[2]}-\phi^{[2,3]})} + \alpha_2 c_2^{[2]} e^{\alpha_2(\phi^{[2]}-\phi^{[2,3]})} = 0,\\
&\alpha_1 c_1^{[3]} e^{\alpha_1(\phi^{[3]}-\phi^{[3,3]})} + \alpha_2 c_2^{[3]} e^{\alpha_2(\phi^{[3]}-\phi^{[3,3]})} = 0;\\
&\alpha_1 c_1^{[3]} e^{\alpha_1(\phi^{[3]}-\phi^{[3,4]})} + \alpha_2 c_2^{[3]} e^{\alpha_2(\phi^{[3]}-\phi^{[3,4]})} + 2Q_4 = 0,\\
&\alpha_1 c_1^{[4]} e^{\alpha_1(\phi^{[4]}-\phi^{[4,4]})} + \alpha_2 c_2^{[4]} e^{\alpha_2(\phi^{[4]}-\phi^{[4,4]})} + 2Q_4 = 0;\\
&\alpha_1 c_1^{[4]} e^{\alpha_1(\phi^{[4]}-\phi^{[4,5]})} + \alpha_2 c_2^{[4]} e^{\alpha_2(\phi^{[4]}-\phi^{[4,5]})} = 0,\\
&\alpha_1 R_1 e^{-\alpha_1\phi^R} + \alpha_2 R_2 e^{-\alpha_2\phi^R} = 0.
\end{aligned}$$

For $\alpha_1 = 2$ and $\alpha_2 = -1$, the electroneutrality condition requires $2L_1 = L_2$ and $2R_1 = R_2$. Therefore,

$$\begin{aligned}
\phi^L =& \nu_0, \\
\phi^{[1,1]} =& \phi^{[1]} - \frac{1}{3}\ln\frac{c_2^{[1]}}{2c_1^{[1]}}, \quad \phi^{[1,2]} = \phi^{[1]} - \ln d_1, \\
\phi^{[2,2]} =& \phi^{[2]} - \ln d_2, \quad \phi^{[2,3]} = \phi^{[2]} - \frac{1}{3}\ln\frac{c_2^{[2]}}{2c_1^{[2]}}, \\
\phi^{[3,3]} =& \phi^{[3]} - \frac{1}{3}\ln\frac{c_2^{[3]}}{2c_1^{[3]}}, \quad \phi^{[3,4]} = \phi^{[3]} - \ln d_3, \\
\phi^{[4,4]} =& \phi^{[4]} - \ln d_4, \quad \phi^{[4,5]} = \phi^{[4]} - \frac{1}{3}\ln\frac{c_2^{[4]}}{2c_1^{[4]}}, \\
\phi^R =& 0,
\end{aligned} \tag{4.9}$$

where d_j's are, respectively, the real roots of

$$2c_1^{[j]}y^3 + 2Q_j y - c_2^{[j]} = 0,$$

where $Q_1 := Q_2$ and $Q_3 := Q_4$. The formula for a real root of the cubic equation $z^3 = 3pz + 2q$ is

$$z = \left(q + \sqrt{q^2 - p^3}\right)^{1/3} + \left(q - \sqrt{q^2 - p^3}\right)^{1/3}.$$

Therefore,

$$d_j = \left(\frac{c_2^{[j]}}{4c_1^{[j]}} + \sqrt{\left(\frac{c_2^{[j]}}{4c_1^{[j]}}\right)^2 + \left(\frac{Q_j}{3c_1^{[j]}}\right)^3}\right)^{1/3} + \left(\frac{c_2^{[j]}}{4c_1^{[j]}} - \sqrt{\left(\frac{c_2^{[j]}}{4c_1^{[j]}}\right)^2 + \left(\frac{Q_j}{3c_1^{[j]}}\right)^3}\right)^{1/3}.$$

Set

$$L = (2L_1)^{1/3} L_2^{2/3},\ R = (2R_1)^{1/3} R_2^{2/3},\ z_j = \left(2c_1^{[j]}\right)^{1/3} \left(c_2^{[j]}\right)^{2/3}.$$

Then, for $j = 1,2,3,4$,

$$c_1^{[j]} = \frac{z_j^3}{2\left(c_2^{[j]}\right)^2}, \quad d_j = \frac{c_2^{[j]}}{z_j} q_j, \tag{4.10}$$

where

$$q_j = \left(\frac{1}{2} + \sqrt{\frac{1}{4} + \frac{8Q_j^3}{27z_j^3}}\right)^{1/3} + \left(\frac{1}{2} - \sqrt{\frac{1}{4} + \frac{8Q_j^3}{27z_j^3}}\right)^{1/3}.$$

4.1.4 Matching of u's at x_j's.

At $x = x_1$, we have two values $u^{[1,l]}$ and $u^{[1,r]}$ for u obtained by solving the boundary value problems on the intervals $(0, x_1)$ and (x_1, x_2), respectively. They are given by

$$\begin{aligned}
u^{[1,l]} =& [\mathrm{sgn}(1,l)]\sqrt{2(c_1^{[1]} + c_2^{[1]} - c_1^{[1]} e^{2\phi^{[1]} - 2\phi^{[1,1]}} - c_2^{[1]} e^{\phi^{[1,1]} - \phi^{[1]}})}, \\
u^{[1,r]} =& [\mathrm{sgn}(1,r)]\sqrt{2(c_1^{[1]} + c_2^{[1]} - c_1^{[1]} e^{2\phi^{[1]} - 2\phi^{[1,2]}} - c_2^{[1]} e^{\phi^{[1,2]} - \phi^{[1]}} - 2Q_2(\phi^{[1]} - \phi^{[1,2]}))},
\end{aligned}$$

where $\mathrm{sgn}(1,l) = \mathrm{sgn}(\phi^{[1]} - \phi^{[1,1]})$ and $\mathrm{sgn}(1,r) = \mathrm{sgn}(\phi^{[1,2]} - \phi^{[1]})$.

Similarly, at $x = x_2$, $x = x_3$ and $x = x_4$,

$$\begin{aligned}
u^{[2,l]} =& [\mathrm{sgn}(2,l)]\sqrt{2(c_1^{[2]} + c_2^{[2]} - c_1^{[2]} e^{2\phi^{[2]} - 2\phi^{[2,2]}} - c_2^{[2]} e^{\phi^{[2,2]} - \phi^{[2]}} - 2Q_2(\phi^{[2]} - \phi^{[2,2]}))}, \\
u^{[2,r]} =& [\mathrm{sgn}(2,r)]\sqrt{2(c_1^{[2]} + c_2^{[2]} - c_1^{[2]} e^{2\phi^{[2]} - 2\phi^{[2,3]}} - c_2^{[2]} e^{\phi^{[2,3]} - \phi^{[2]}})},
\end{aligned}$$

where $\mathrm{sgn}(2,l) = \mathrm{sgn}(\phi^{[2]} - \phi^{[2,2]})$ and $\mathrm{sgn}(2,r) = \mathrm{sgn}(\phi^{[2,3]} - \phi^{[2]})$.

Upon the matchings $u^{[j,l]} = u^{[j,r]}$ for $j = 1,2,3,4$, we get

$$c_1^{[j]}\left(\frac{c_2^{[j]}}{2c_1^{[j]}}\right)^{2/3} + c_2^{[j]}\left(\frac{2c_1^{[j]}}{c_2^{[j]}}\right)^{1/3} = c_1^{[j]}d_j^2 + c_2^{[j]}d_j^{-1} + 2Q_j \ln d_j.$$

In view of (4.10), the above system is reduced to, for $j = 1,2,3,4$,

$$c_2^{[j]} = \frac{z_j}{q_j}\exp\left\{\frac{(3q_j - 2q_j^2 - 2)z_j}{4q_jQ_j}\right\}. \tag{4.11}$$

4.1.5 Matching of J_i's over each subinterval.

For $1 \le j \le 5$, set $H_j = \int_{x_{j-1}}^{x_j} h^{-1}(s)ds$. Over (x_0,x_1), (x_2,x_3) and (x_4,x_5), the flux densities J_1 and J_2 are given by, respectively,

$$\begin{aligned}
J_1 &= \frac{c_1^L - c_1^{[1,1]}}{H_1}\left(1 + \frac{2\phi^L - 2\phi^{[1,1]}}{\ln c_1^L - \ln c_1^{[1,1]}}\right),\\
J_2 &= \frac{c_2^L - c_2^{[1,1]}}{H_1}\left(1 - \frac{\phi^L - \phi^{[1,1]}}{\ln c_2^L - \ln c_2^{[1,1]}}\right);\\
J_1 &= \frac{c_1^{[2,3]} - c_1^{[3,3]}}{H_3}\left(1 + \frac{2\phi^{[2,3]} - 2\phi^{[3,3]}}{\ln c_1^{[2,3]} - \ln c_1^{[3,3]}}\right),\\
J_2 &= \frac{c_2^{[2,3]} - c_2^{[3,3]}}{H_3}\left(1 - \frac{\phi^{[2,3]} - \phi^{[3,3]}}{\ln c_2^{[2,3]} - \ln c_2^{[3,3]}}\right);\\
J_1 &= \frac{c_1^{[4,5]} - c_1^R}{H_5}\left(1 + \frac{2\phi^{[4,5]} - 2\phi^R}{\ln c_1^{[4,5]} - \ln c_1^R}\right),\\
J_2 &= \frac{c_2^{[4,5]} - c_2^R}{H_5}\left(1 - \frac{\phi^{[4,5]} - \phi^R}{\ln c_2^{[4,5]} - \ln c_2^R}\right).
\end{aligned}$$

Over (x_1,x_2) and (x_3,x_4), the flux densities J_1 and J_2 are determined through, re-

spectively,

$$
\begin{aligned}
\phi^{[2,2]} &= \phi^{[1,2]} - (2J_1 - J_2)y_1, \\
c_1^{[2,2]} &= e^{-2(J_1+J_2)y_1} c_1^{[1,2]} - \frac{Q_2 J_1}{2(J_1+J_2)} \left(1 - e^{-2(J_1+J_2)y_1}\right), \\
J_1 + J_2 &= \frac{6(c_1^{[1,2]} - c_1^{[2,2]}) - 2Q_2(\phi^{[1,2]} - \phi^{[2,2]})}{2H_2}, \\
\phi^{[4,4]} &= \phi^{[3,4]} - (2J_1 - J_2)y_2, \\
c_1^{[4,4]} &= e^{-2(J_1+J_2)y_2} c_1^{[3,4]} - \frac{Q_4 J_1}{2(J_1+J_2)} \left(1 - e^{-2(J_1+J_2)y_2}\right), \\
J_1 + J_2 &= \frac{6(c_1^{[3,4]} - c_1^{[4,4]}) - 2Q_4(\phi^{[3,4]} - \phi^{[4,4]})}{2H_4}.
\end{aligned}
$$

Recall that

$$
\begin{aligned}
c_1^L &= \frac{L}{2}, \quad c_2^L = 2c_1^L = L, \\
c_1^{[1,1]} &= \frac{z_1}{2}, \quad c_2^{[1,1]} = 2c_1^{[1,1]} = z_1, \\
c_1^{[2,3]} &= \frac{z_2}{2}, \quad c_2^{[2,3]} = 2c_1^{[2,3]} = z_2, \\
c_1^{[3,3]} &= \frac{z_3}{2}, \quad c_2^{[3,3]} = 2c_1^{[3,3]} = z_3, \\
c_1^{[4,5]} &= \frac{z_4}{2}, \quad c_2^{[4,5]} = 2c_1^{[4,5]} = z_4, \\
c_1^R &= \frac{R}{2}, \quad c_2^R = 2c_1^R = R,
\end{aligned}
$$

and

$$
\begin{aligned}
c_1^{[1,2]} &= d_1^2 c_1^{[1]}, \quad c_2^{[1,2]} = 2c_1^{[1,2]} + 2Q_2 = 2d_1^2 c_1^{[1]} + 2Q_2, \\
c_1^{[2,2]} &= d_2^2 c_1^{[2]}, \quad c_2^{[2,2]} = 2c_1^{[2,2]} + 2Q_2 = 2d_2^2 c_1^{[2]} + 2Q_2, \\
c_1^{[3,4]} &= d_3^2 c_1^{[3]}, \quad c_2^{[3,4]} = 2c_1^{[3,4]} + 2Q_4 = 2d_3^2 c_1^{[3]} + 2Q_4, \\
c_1^{[4,4]} &= d_4^2 c_1^{[4]}, \quad c_2^{[4,4]} = 2c_1^{[4,4]} + 2Q_4 = 2d_4^2 c_1^{[4]} + 2Q_4.
\end{aligned}
$$

Therefore,

$$
\begin{aligned}
J_1 &= \frac{L - z_1}{H_1} \left(\frac{1}{2} + \frac{\nu_0 - \phi^{[1]} + \ln c_2^{[1]} - \ln z_1}{\ln L - \ln z_1} \right), \\
J_2 &= \frac{L - z_1}{H_1} \left(1 - \frac{\nu_0 - \phi^{[1]} + \ln c_2^{[1]} - \ln z_1}{\ln L - \ln z_1} \right); \\
J_1 &= \frac{z_2 - z_3}{H_3} \left(\frac{3}{2} + \frac{\phi^{[2]} - \phi^{[3]} - \ln c_2^{[2]} + \ln c_2^{[3]}}{\ln z_2 - \ln z_3} \right), \\
J_2 &= \frac{z_2 - z_3}{H_3} \left(- \frac{\phi^{[2]} - \phi^{[3]} - \ln c_2^{[2]} + \ln c_2^{[3]}}{\ln z_2 - \ln z_3} \right); \\
J_1 &= \frac{z_4 - R}{H_5} \left(\frac{1}{2} + \frac{\phi^{[4]} - \ln c_2^{[4]} + \ln z_4}{\ln z_4 - \ln R} \right), \\
J_2 &= \frac{z_4 - R}{H_5} \left(1 - \frac{\phi^{[4]} - \ln c_2^{[4]} + \ln z_4}{\ln z_4 - \ln R} \right).
\end{aligned}
$$

In particular,

$$
J_1 + J_2 = \frac{3(L - z_1)}{2H_1} = \frac{3(z_2 - z_3)}{2H_3} = \frac{3(z_4 - R)}{2H_5},
$$

and hence,

$$
z_2 = z_3 + \frac{H_3}{H_1}(L - z_1), \quad z_4 = R + \frac{H_5}{H_1}(L - z_1).
$$

Also

$$
\begin{aligned}
\phi^{[2]} - \ln d_2 &= \phi^{[1]} - \ln d_1 - (2J_1 - J_2)y_1, \\
d_2^2 c_1^{[2]} &= d_1^2 e^{-2(J_1+J_2)y_1} c_1^{[1]} - \frac{Q_2 J_1}{2(J_1+J_2)} \left(1 - e^{-2(J_1+J_2)y_1}\right), \\
J_1 + J_2 &= \frac{6(d_1^2 c_1^{[1]} - d_2^2 c_1^{[2]}) - 2Q_2(\phi^{[1]} - \phi^{[2]} - \ln d_1 + \ln d_2)}{2H_2}, \\
\phi^{[4]} - \ln d_4 &= \phi^{[3]} - \ln d_3 - (2J_1 - J_2)y_2, \\
d_4^2 c_1^{[4]} &= d_3^2 e^{-2(J_1+J_2)y_2} c_1^{[3]} - \frac{Q_4 J_1}{2(J_1+J_2)} \left(1 - e^{-2(J_1+J_2)y_2}\right), \\
J_1 + J_2 &= \frac{6(d_3^2 c_1^{[3]} - d_4^2 c_1^{[4]}) - 2Q_4(\phi^{[3]} - \phi^{[4]} - \ln d_3 + \ln d_4)}{2H_4}.
\end{aligned}
$$

From different expressions of $J_1 + J_2$ above, one has

$$
\begin{aligned}
\phi^{[2]} =& \phi^{[1]} - \ln \frac{d_1}{d_2} + \frac{3H_2(L - z_1)}{2H_1 Q_2} - \frac{3(d_1^2 c_1^{[1]} - d_2^2 c_1^{[2]})}{Q_2}, \\
\phi^{[4]} =& \phi^{[3]} - \ln \frac{d_3}{d_4} + \frac{3H_4(L - z_1)}{2H_1 Q_4} - \frac{3(d_3^2 c_1^{[3]} - d_4^2 c_1^{[4]})}{Q_4}, \\
\phi^{[4]} =& \frac{H_5(L - z_1)\ln z_4/R}{H_1(z_4 - R)\ln L/z_1} \left(\nu_0 - \phi^{[1]} + \ln c_2^{[1]} - \frac{3}{2}\ln z_1 + \frac{1}{2}\ln L\right) \\
& + \ln c_2^{[4]} - \frac{3}{2}\ln z_4 + \frac{1}{2}\ln R, \\
\phi^{[2]} =& \phi^{[3]} + \ln \frac{c_2^{[2]}}{c_2^{[3]}} - \frac{3}{2}\ln \frac{z_2}{z_3} \\
& + \frac{H_3(L - z_1)\ln z_2/z_3}{H_1(z_2 - z_3)\ln L/z_1} \left(\nu_0 - \phi^{[1]} + \ln c_2^{[1]} - \frac{3}{2}\ln z_1 + \frac{1}{2}\ln L\right).
\end{aligned}
$$

Therefore,

$$\begin{aligned}
\phi^{[3]} =& \frac{H_5(L-z_1)\ln z_4/R}{H_1(z_4-R)\ln L/z_1}\left(\nu_0-\phi^{[1]}+\ln c_2^{[1]}-\frac{3}{2}\ln z_1+\frac{1}{2}\ln L\right)\\
&+\ln c_2^{[4]}-\frac{3}{2}\ln z_4+\frac{1}{2}\ln R,\\
&+\ln\frac{d_3}{d_4}-\frac{3H_4(L-z_1)}{2H_1Q_4}+\frac{3(d_3^2c_1^{[3]}-d_4^2c_1^{[4]})}{Q_4},\\
\phi^{[2]} =& \frac{H_5(L-z_1)\ln z_4/R}{H_1(z_4-R)\ln L/z_1}\left(\nu_0-\phi^{[1]}+\ln c_2^{[1]}-\frac{3}{2}\ln z_1+\frac{1}{2}\ln L\right)\\
&+\frac{H_3(L-z_1)\ln z_2/z_3}{H_1(z_2-z_3)\ln L/z_1}\left(\nu_0-\phi^{[1]}+\ln c_2^{[1]}-\frac{3}{2}\ln z_1+\frac{1}{2}\ln L\right)\\
&+\ln\frac{d_3}{d_4}-\frac{3H_4(L-z_1)}{2H_1Q_4}+\frac{3(d_3^2c_1^{[3]}-d_4^2c_1^{[4]})}{Q_4},\\
&+\ln\frac{c_2^{[2]}}{c_2^{[3]}}-\frac{3}{2}\ln\frac{z_2}{z_3}+\ln c_2^{[4]}-\frac{3}{2}\ln z_4+\frac{1}{2}\ln R.
\end{aligned}$$

So,

$$\begin{aligned}
\phi^{[1]} =& \frac{E}{1+E}\left(\nu_0+\ln c_2^{[1]}-\frac{3}{2}\ln z_1+\frac{1}{2}\ln L\right)+\frac{1}{1+E}\ln\frac{d_1d_3c_2^{[2]}c_2^{[4]}}{d_2d_4c_2^{[3]}R}\\
&+\frac{3}{2(1+E)}\ln\frac{z_3R}{z_2z_4}-\frac{3H_2(L-z_1)}{2H_1Q_2(1+E)}-\frac{3H_4(L-z_1)}{2H_1Q_4(1+E)}\\
&+\frac{3(d_1^2c_1^{[1]}-d_2^2c_1^{[2]})}{Q_2(1+E)}+\frac{3(d_3^2c_1^{[3]}-d_4^2c_1^{[4]})}{Q_4(1+E)},
\end{aligned}\tag{4.12}$$

where

$$E=\frac{H_5(L-z_1)\ln z_4/R}{H_1(z_4-R)\ln L/z_1}+\frac{H_3(L-z_1)\ln z_2/z_3}{H_1(z_2-z_3)\ln L/z_1}.$$

Note that every term on the right-hand-side of (4.12) can be expressed explicitly in terms of z_1 and z_3. Hence, J_1, J_2, y_1 and y_2 can be expressed in terms of z_1 and z_3. We

therefore deduce two equations for z_1 and z_3 as

$$d_2^2 c_1^{[2]} = d_1^2 e^{-2(J_1+J_2)y_1} c_1^{[1]} - \frac{Q_2 J_1}{2(J_1+J_2)} \left(1 - e^{-2(J_1+J_2)y_1}\right),$$
$$d_4^2 c_1^{[4]} = d_3^2 e^{-2(J_1+J_2)y_2} c_1^{[3]} - \frac{Q_4 J_1}{2(J_1+J_2)} \left(1 - e^{-2(J_1+J_2)y_2}\right).$$

4.2 Numerical and Analytical Results of I-V Relations

We consider the system as described in (4.3). In this section we use *KCl*, dissociating into K^+ and Cl^- ions, as an example for molecules transported across the channel. The area function $h(x)$ is denoted by assuming tubular shape at any $x \in [0,1]$ (i.e. $h(x) = \pi r^2$) with the following radius:

$$\begin{aligned}
r = 12, \quad for \quad x \in [0, 0.25),\\
r = 6, \quad for \quad x \in [0.25, 0.5),\\
r = 3.5, \quad for \quad x \in [0.5, 0.625),\\
r = 3.5, \quad for \quad x \in [0.625, 0.775),\\
r = 7.5, \quad for \quad x \in [0.775, 1],
\end{aligned}$$

and the permanent charges are defined as:

$$\begin{aligned}
Q = 0, \quad for \quad x \in [0, 0.25),\\
Q = -1.5, \quad for \quad x \in [0.25, 0.5),\\
Q = 0, \quad for \quad x \in [0.5, 0.625),\\
Q = -4, \quad for \quad x \in [0.625, 0.775),\\
Q = 0, \quad for \quad x \in [0.775, 1].
\end{aligned}$$

Other parameters include: $\varepsilon^2 = 0.039$, $D_1 = 6.91 \times 10^{-11}$ for K^+ and $D_2 = 9.00 \times 10^{-11}$ for Cl^-. The concentrations of KCl in all cases are represented in the unit of mM and the voltage, Φ_Δ, in mV. The current calculated using analytical and numerical methods is denoted in pA.

The results are plotted and shown in the following figures.

$[KCl]$ = 1000/100 mM (in/out), shown in Figure 4.1.

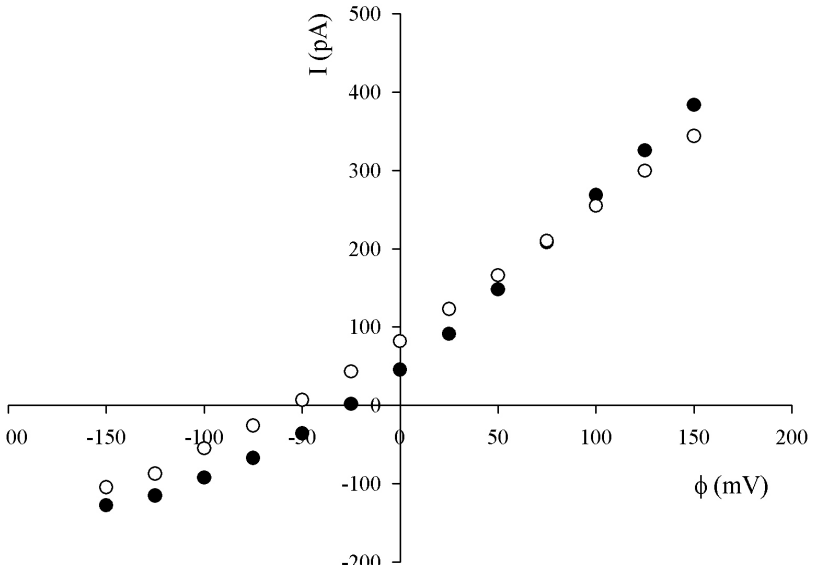

Figure 4.1. Comparison of I-V relation for 1000/100 mM KCl. Analytical results are shown in filled circles and numerical results in open circles.

$[KCl]$ = 250/250 mM (in/out), shown in Figure 4.2.

These figures indicate that the numerical results are in good approximation to the analytical solutions as well as the well characterized I-V relations obtained under experimental conditions ([13]).

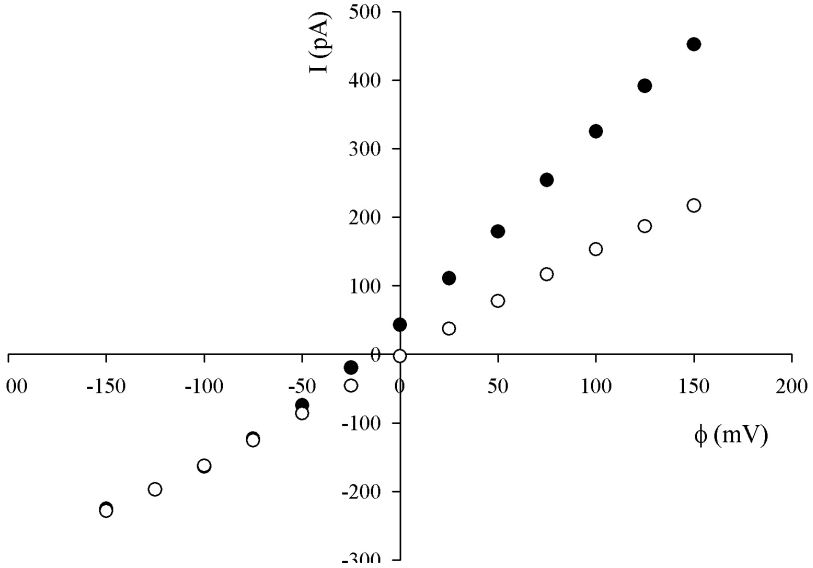

Figure 4.2. Comparison of I-V relation for $250/250$ *mM KCl*. Analytical results are shown in filled circles and numerical results in open circles.

Chapter 5

Concluding Remarks

The event of ion flow under steady-state conditions through a specific type of membrane bound protein, ion channel, is governed by the Poisson-Nernst-Planck equations. We have shown that the one-dimensional Poisson-Nernst-Planck system can be explicitly solved when two types of ions flow simultaneously. The analytical results indicate the existance of multiple solutions and this leads to multiple numerical solutions when solving the system on three intervals ($[0, 1/3]$, $[1/3, 2/3]$ and $[2/3, 1]$). These solutions, however, all converge to one stable solution when used as initial values to solve the PNP system on $[0, 1]$. The multiple solutions resulting from analytical method might indicate a direct reflection of more complicated behaviors of ion channels such as gating mechanisms. More investigation through numerical means are needed to draw further conclusions. The effect of a small parameter ε is also studied. The result indicates that as ε decreases the faster changing layer can be found. This confirms the findings of functional analysis when considering sigularly perturbed PNP systems.

The PNP system describing the flow of three types of ions is more complicated and involves more parameters. The analytical solutions are not available at this time, but the system can be solved numerically. The results, although priliminary, show evidence

of a correlation between the ion distribution and boundary conditions. This could indicate the ability of an ion channel to discriminate among ions and to selectively allow passage of a certain type of ion. It has been observed in experimental research that the permanent charges located inside the channel contribute significantly to the ion selectivity. The methods described in this thesis may be applied to the investigation of ion properties with one great advantage, that is, both analytical and numerical methods can resolve ion distribution at any partcular point along the channel while no experimental procedure permits that.

The current-voltage (I-V) relation is a physical indication of the flow capacity allowed by an ion channel. The I-V relation of a KCl type ion channel is revealed in this thesis using both analytical and numerical methods, which give very comparable outcomes. These methods can be utilized to gain information required for experimental designs. Another possible application of the numerical method is that it can be used to determine the permanent charge properties through an optimization procedure and usage of the experimental data.

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